X Applicant's copy 09/836,804

ACCESSION NUMBER: 96294739 MEDLINE
DOCUMENT NUMBER: 96294739 PubMed ID: 8698454
TITLE: Bacterially induced bone destruction: mechanisms and misconceptions.
AUTHOR: Nair S P; Meghji S; Wilson M; Reddi K; White P; Henderson B
CORPORATE SOURCE: Maxillofacial Surgery Research Unit, Eastman Dental Insitute, University College London, United Kingdom.
SOURCE: INFECTION AND IMMUNITY, (1996 Jul) 64 (7) 2371-80. Ref: 137
Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960912
Last Updated on STN: 19960912
Entered Medline: 19960904

AB Normal bone remodelling requires the coordinated regulation of the genesis and activity of osteoblast and osteoclast lineages. Any interference with these integrated cellular systems can result in dysregulation of remodelling with the consequent loss of bone matrix. **Bacteria** are important causes of bone pathology in common conditions such as periodontitis, dental cysts, **bacterial** arthritis, and osteomyelitis. It is now established that many of the **bacteria** implicated in **bone diseases** contain or produce molecules with potent effects on bone cells. Some of these molecules, such as components of the gram-positive cell walls (lipoteichoic acids), are weak stimulators of bone resorption in vitro, while others (PMT, cpn60) are as active as the most active mammalian osteolytic factors such as cytokines like IL-1 and TNF. The complexity of the integration of bone cell lineage development means that there are still question marks over the mechanism of action of many well-known bone-modulatory molecules such as parathyroid hormone. The key questions which must be asked of the now-recognized **bacterial** bone-modulatory molecules are as follows: (i) what cell population do they bind to, (ii) what is the nature of the receptor and postreceptor events, and (iii) is their action direct or dependent on the induction of secondary extracellular bone-modulating factors such as cytokines, eicosanoids, etc. In the case of LPS, this ubiquitous gram-negative polymer probably binds to osteoblasts or other cells in bone through the CD14 receptor and stimulates them to release cytokines and eicosanoids which then induce the recruitment and activation of osteoclasts. This explains the inhibitor effects of nonsteroidal and anticytokine agents on LPS-induced bone resorption. However, other **bacterial** factors such as the potent toxin PMT may act by blocking the normal maturation pathway of the osteoblast lineage, thus inducing dysregulation in the tightly regulated process of resorption and replacement of bone matrix. At the present time, it is not possible to define a general mechanism by which **bacteria** promote loss of bone matrix. Many **bacteria** are capable of stimulating bone matrix loss, and the information available would suggest that each organism possesses different factors which interact with bone in different

ways. With the rapid increase in antibiotic resistance, particularly with Staphylococcus aureus and M. tuberculosis, organisms responsible for much bone pathology in developed countries only two generations ago, we would urge that much greater attention should be focused on the problem of **bacterially** induced bone remodelling in order to define pathogenetic mechanisms which could be therapeutic targets for the development of new treatment modalities.

AB . . . Any interference with these integrated cellular systems can result in dysregulation of remodelling with the consequent loss of bone matrix. **Bacteria** are important causes of bone pathology in common conditions such as periodontitis, dental cysts, **bacterial** arthritis, and osteomyelitis. It is now established that many of the **bacteria** implicated in **bone diseases** contain or produce molecules with potent effects on bone cells. Some of these molecules, such as components of the gram-positive. . . action of many well-known bone-modulatory molecules such as parathyroid hormone. The key questions which must be asked of the now-recognized **bacterial** bone-modulatory molecules are as follows: (i) what cell population do they bind to, (ii) what is the nature of the. . . and activation of osteoclasts. This explains the inhibitor effects of nonsteroidal and anticytokine agents on LPS-induced bone resorption. However, other **bacterial** factors such as the potent toxin PMT may act by blocking the normal maturation pathway of the osteoblast lineage, thus. . . and replacement of bone matrix. At the present time, it is not possible to define a general mechanism by which **bacteria** promote loss of bone matrix. Many **bacteria** are capable of stimulating bone matrix loss, and the information available would suggest that each organism possesses different factors which. . . developed countries only two generations ago, we would urge that much greater attention should be focused on the problem of **bacterially** induced bone remodelling in order to define pathogenetic mechanisms which could be therapeutic targets for the development of new treatment. . .

AB . . . tomography (CT) and magnetic resonance imaging (MRI) scans. Operations included transarticular screw fixation in all cases; in patients with rheumatoid **arthritis** it was associated with sublaminar fixation and **bone** grafting following Sonntag's technique in all but two cases. Postoperative results were evaluated in relation to the biomechanical stability and. . .

L10 ANSWER 2 OF 1695 MEDLINE
AB . . . together with low gastrointestinal toxicity in animal models. It is a potent inhibitor not only of acute exudation in adjuvant **arthritis** in the rat, but also of **bone** and cartilage destruction. The therapeutic range of meloxicam in the rat, with regard to
inhibition of adjuvant arthritis, was several. . .

L10 ANSWER 3 OF 1695 MEDLINE
AB . . . (mean 21.5 years). Four of the 10 patients with mild deformity exhibited prominent soft tissue pathology, with minimal destruction of **bone**; the other 6 patients had bony alterations that resembled rheumatoid **arthritis**. CONCLUSION: In SLE patients with arthritis of the finger joints, MRI detects characteristic signs of soft tissue pathology (e.g., capsular. . .

L10 ANSWER 4 OF 1695 MEDLINE
TI Mice missing enzyme suffer dwarfism, thin **bones**, and **arthritis**.

L10 ANSWER 5 OF 1695 MEDLINE
AB IL-7, a powerful lymphopoietic cytokine, is elevated in rheumatoid **arthritis** (RA) and known to induce **bone** loss when administered in vivo. IL-7 has been suggested to induce bone loss, in part, by stimulating the proliferation of. . .

L8 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:798038 CAPLUS
DOCUMENT NUMBER: 135:339263
TITLE: Use of thioamide oxazolidinones for the treatment of **bone** resorption and **osteoporosis**
INVENTOR(S): Mesfin, Gebre-Mariam; Jensen, Richard K.
PATENT ASSIGNEE(S): Pharmacia + Upjohn Company, USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001080841	A2	20011101	WO 2001-US10805	20010417
WO 2001080841	A3	20020404		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002010341	A1	20020124	US 2001-836804	20010417
EP 1274426	A2	20030115	EP 2001-926589	20010417
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-198688P P 20000420
WO 2001-US10805 W 20010417
OTHER SOURCE(S): MARPAT 135:339263

L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:350596 CAPLUS
DOCUMENT NUMBER: 131:724
TITLE: Use of oxazolidinone derivatives for treating psoriasis and arthritis and reducing the toxicity of cancer chemotherapy
INVENTOR(S): Batts, Donald H.; Ulrich, Roger G.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925344	A1	19990527	WO 1998-US23233	19981110
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2303961	AA	19990527	CA 1998-2303961	19981110
AU 9915823	A1	19990607	AU 1999-15823	19981110
AU 743941	B2	20020207		
EP 1032386	A1	20000906	EP 1998-960157	19981110
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BR 9815615	A	20001024	BR 1998-15615	19981110
JP 2001522886	T2	20011120	JP 2000-520777	19981110

PRIORITY APPLN. INFO.:

US 1997-65689P	P	19971118
US 1998-71297P	P	19980116
US 1998-73662P	P	19980204
US 1998-75247P	P	19980219
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WO 1998-US23233	W	19981110

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AI		
AU 1998-74883	A	19980513
AU 1998-74883	A	19980518
BR 1998-15518	A	19980518
CN 1998-805423	A	19980518
EP 1998-922303	A	19980518
FI 1999-2555	A	19991130
HU 2000-1393	A	19980518
JP 1999-500722	A	19980518
NO 1999-5846	A	19991129
NZ 1998-501412	A	19980518
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SK 1999-1564	A	19980518
US 1998-200904	A	19981127
US 1998-80751	A	19980518
US 2000-712055	A	20001114
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US 2001-822666	A	20010330
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AU 9874883	A1	19981230
AU 737995	B2	20010906
BR 9815518	A	20001121
CN 1257486	T	20000621
EP 984947	A1	20000315
FI 9902555	A	19991130
HU 2000001393	AB	20010628
JP 2002501530	T2	20020115
NO 9905846	A	20000128
NO 9905846	A0	19991129
NZ 501412	A	20011130
PL 337329	A1	20000814
SK 9901564	A3	20000612
US 6255304 X	BA	20010703
US 6218413 X	BA	20010417
US 6362189 X	BA	20020326
US 6342513	BA	20020129
US 2001041728 X	AA	20011115
US 2002016323	AA	20020207
WO 9854161	A1	19981203
WO 9854161	C2	19990408

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L2         38753 S E1-E106

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L3             1 S 168828-65-7/RN

     FILE 'REGISTRY' ENTERED AT 11:14:21 ON 15 OCT 2001
L4             1 S 172966-53-9/RN

     FILE 'REGISTRY' ENTERED AT 11:14:58 ON 15 OCT 2001
L5             1 S 181996-80-5/RN

     FILE 'REGISTRY' ENTERED AT 11:15:36 ON 15 OCT 2001
L6             1 S 188974-73-4/RN

     FILE 'REGISTRY' ENTERED AT 11:16:04 ON 15 OCT 2001
L7             1 S 216868-57-4/RN

     FILE 'REGISTRY' ENTERED AT 11:17:02 ON 15 OCT 2001
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L10            1 S 216868-99-4/RN

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L19           45 S L18 NOT PY>=2000
L20           57 S (ANTIBACTERIAL OR BACTERIA?)(L)(BONE(W)(DISEASE# OR
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L21           46 S L20 NOT PY>=2000
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L22   ANSWER 1 OF 1  INPADOC  COPYRIGHT 2001 EPO

PATENT FAMILY INFORMATION
 AN   49077735 INPADOC

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                                       BR 1998-15518        A  19980518
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                                       SK 1999-1564         A  19980518
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 US 1998-80751        A  19980518      US 1998-80751        A  19980518
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 AU 1998-74883        A  19980513      AU 9874883           A1 19981230
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 HU 2000-1393         A  19980518      HU 2000001393        AB 20010628
 NO 1999-5846         A  19991129      NO 9905846           A  20000128
                                       NO 9905846           A0 19991129
 PL 1998-337329       A  19980518      PL 337329            A1 20000814
 SK 1999-1564         A  19980518      SK 9901564           A3 20000612
 US 1998-200904       A  19981127      US 6255304           BA 20010703
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                                       WO 9854161           C2 19990408

 5 priorities, 12 applications, 14 publications
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method compounds & composite

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             6 154590-54-2/BI
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